DESIGN AND DEVELOPMENT OF SOME NOVEL MOLECULES TARGETED FOR NEUROPATHIC PAIN

A

SYNOPSIS

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ANNEXURE I

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INTRODUCTION:-

Neuropathic pain is a complex, chronic pain caused by damage or disease affecting the somatosensory nervous system[1]. With neuropathic pain, the nerve fibers themselves may be damaged, dysfunctional, or injured. These damaged nerve fibers send incorrect signals to other pain centers. The impact of nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury.Neuropathic pain may be associated with abnormal sensations called dysesthesia or pain from normally non-painful stimuli (allodynia).

Up to 7% to 8% of the European population is affected, and in 5% of persons it may be severe[2, 3]. Neuropathic pains may result from disorders of the peripheral nervous system or the central nervous system (brain and spinal cord). Thus, neuropathic pain may be divided into peripheral neuropathic pain, central neuropathic pain, or mixed (peripheral and central) neuropathic pain.

Central neuropathic pain is found in spinal cord injury, multiple sclerosis and some strokes[4]. Aside from diabetes (see diabetic neuropathy) and other metabolic conditions, the some common causes of neuropathic pain include:

- Alcoholism
- Amputation
- Back, leg, and hip problems
- Chemotherapy
- Diabetes
- Facial nerve problems
- HIV infection or AIDS
- Multiple sclerosis
- Shingles

- Spine surgery

Neuropathic pain shows symptoms like

- Shooting and burning pain
- Tingling and numbness

Melatonin circulating in mammals is mainly of pineal origin,the hormone is also produced by neuro-endocrine cellsin the retina, pancreas and gastrointestinal tract, in minor amounts by nonendocrine cells such as bone marrow,thymus and lymphocytes, where it may be of some localimportance.The biosynthesis of Melatonin(MLT) in the pineal gland involves severalsteps that can be summarized as follows: pinealocytes take up L-tryptophan from the cerebral vessels and convert it to serotonin through 5-hydroxylation and decarboxylation; serotonin is thenconverted to *N*-acetyl-serotonin by the rate-limiting enzyme arylalkylamine-*N*-acetyl transferase, before finally being converted into MLT by hydroxyindole-*O*-methyl transferase. Once synthesized, MLT is not stored within the pineal gland,but diffuses out into the bloodstream, rapidly reaching all tissuesof the body.

Melatonin (N-acetyl-5-methoxytryptamine, MLT) is the main neuro hormone produce in different tissues preliminary in the pineal gland, retina and gastrointestinal tract. Beyond its fundamental role in circadian and seasonal rhythms regulation.The highest level of melatonin occurring during the period of darkness[5].

Melatonin hasbeen involved in variety of physiological such as antioxidant, effective in prevention of numeroustypes of neurodegenerative disorders in which free radicalprocesses are involved. In brief, melatonin has been found toprotect the CNS from beta-amyloid toxicity, glutamate-induced excitotoxicity, nitric oxide toxicity, cyanide toxicity and ischemia/reperfusion

injury. It is also produce in plants where it functions as first line of defense against oxidative stress.

Different class of melatonin receptor are found MT_1, MT_2& MT_3 receptor depending upon this various melatonin receptor ligand have been recently reported. They have been designed on the basis of the structural similarity with Indole and other naphthalene analogs.

It is well known that indole derivatives,extensively present in natural compounds and are very important substances in medicinal and biological aspects. The antioxidant effect of indole ring carrier melatonin has been well described.The development of synthetic compounds capable of mimickingtheeffects of melatonin has progressed considerably during thepast decade. These compounds are structurallydiverse and rangedfrom simple indole derivatives and its Bioisosteres, constrained melatoninergic agents [6, 7].

Among the actions attributed to melatonin are those concerning circadianrhythms and sleep regulation, control of mood and behavior, neuro-immunomodulation, blood pressure control, pain perception, anti-inflammatory, antioxidant, neuro-protectant and antitumor of particular interestare also the reports on its putative role in the events leadinto the development of type 2 diabetes.Although many of the miraculous claims made about MLT arematter of speculation, clinical trials and results of preclinical studiesin validated animal models suggest that some therapeutic optionsexist for MLT, particularly for the treatment of insomnia, neuropathic pain,circadian-rhythm sleep disorders (CRSDs), and depression[8].

Indole derivatives constitute an important class of therapeutically agentsinmedicinal chemistry including anticancer, neuroprotective agent, antioxidant, anti-rheumatoid, aldose reeducatesinhibitor and anti-HIV agents.

Oxidative stress has been implicated in the developmentof neurodegenerative diseases like Parkinson's disease, Alzheimer's disease,Huntington's disease, epileptic seizures, stroke, and as a contributor to aging and sometypes of cancer. Indole compounds are very efficient antioxidants, protecting both lipidsand proteins from per oxidation and it is known that the indole structure influences theantioxidant efficacy in biological systems. Due to its free radical scavenger and antioxidantproperties, synthesis of indole derivative compounds are under investigation todetermine which exhibit the highest activity with the lowest side effects. Epidemiologicalstudies have been strongly suggesting that antioxidants can decrease the rate of manydiseases. However, more clinical studies are required to determine the efficacy and safetyof these compounds.

NEED OF STUDY:-

Due to hectic and stressful life style of human being now a day majority of peoples are suffering to chronic diseases such as Diabetes, Cancer and neurodegenerative diseases. Once these chronic diseases occur patient undergoes oxidative stress and after some period person suffer from neuropathic pain.

Pregabalin and Gabapentin reduce pain associated with diabetic neuropathy. The anticonvulsants carbamazepine and oxcarbazepine are especially effective in trigeminal neuralgia. A short trial period of gabapentin therapy is recommended, to determine the effectiveness for that person. Peoples in 62% population taking gabapentin may have at least one adverse event, however the incidence of serious adverse events was found to be low.

Unfortunately, neuropathic pain often responds poorly to standard pain treatments and occasionally may get worse instead of better over time. For some people, it can lead to serious

disability. A multidisciplinary approach that combines therapies, however, can be a very effective way to provide relief from neuropathic pain.

In this process a need to investigate a good scaffold which probably shows a less adverse effect and better biological action is increases[9].

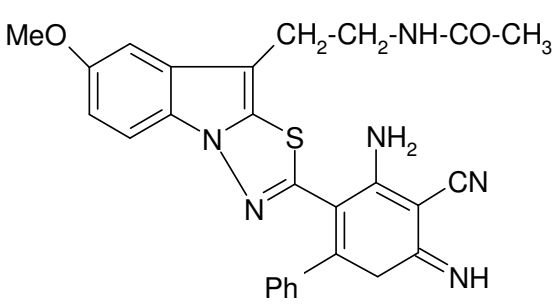
In this association Indole and its structural analogues are suitable pharmacophore are binding with melatonin receptor i.e. MT_1& MT_2 receptor.

As review of literature suggest indole derivatives shows a promising action against neuropathic pain &neurodegenerative diseases.We are planning to synthesize a series of indole derivatives which they are suitably bind with melatonin receptor and shows melatonin receptor agonist agent due to this they are able to show action against neuropathic pain & act as a neuroprotective, anti-oxidant agent[10].

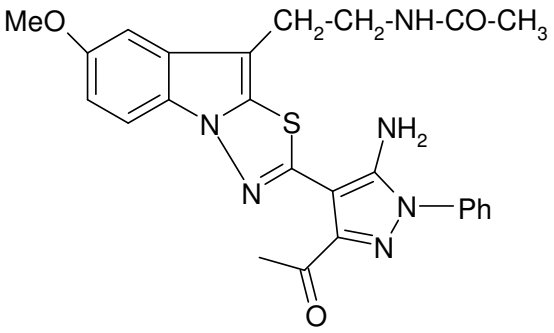
REVIEW OF LITERATURE:-

A considerable amount of information accumulated in the literature survey reveals an approach to verity of synthetic route used by investigator to identify and synthesis of proper pharmacophore with its structural analogues as a melatonin receptor agonist agent.It give a clear idea of synthetic possibilities of one or the other methods.

Hanaa HAet al[11],Synthesized the key compound N-[2-(2-(6-Amino-5-cyano-4-imino-2-phenylcyclohexa-1,5-dienyl)-7-methoxy-1,3,4-thiadiazolo[3,2-a]indol-9-yl)ethyl]acetamide(i) and N-[2-(5-Methoxy-1-(morpholinomethyl)-1H-indol-3-yl)ethyl]acetamide (ii)from 5-methoxy indole which shows a potent neuroprotective agent as an melatonin derivatives on rat animal.

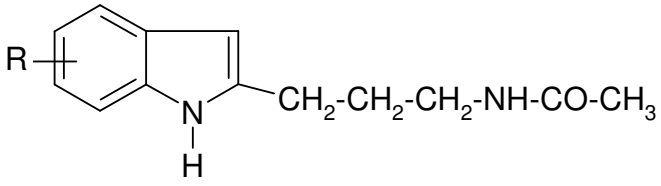


(i)



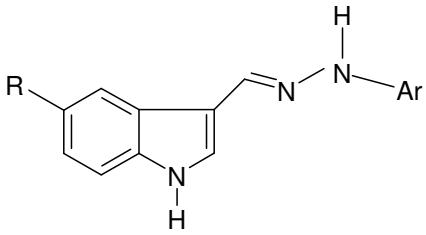
(ii)

Gilberto S et al[12], have synthesized a series of substituted *N*-[3-(1*H*-indol-2-yl)propyl]acetamide (iii) from methyl indole 2-carboxylate shows potent Melatonin receptor agonist action (MT_1).



(iii)

GökceGetal[13],synthesized a series of substituted indole hydrazine (iv) and hydrazide (v) derivatives as a melatonin agonist agent having antioxidant properties, in this work Most of the compounds showed significantly higher activity than MLT at 10^{-3}M and 10^{-4}M concentrations. The structure active relationship suggests a new approach for the *in vitro* Antioxidant activity properties for 3 and 5 substituted indole ring. Lack of methoxy group on 5 position or introductionof Br in the 5-position did not affect the antioxidant capacity.



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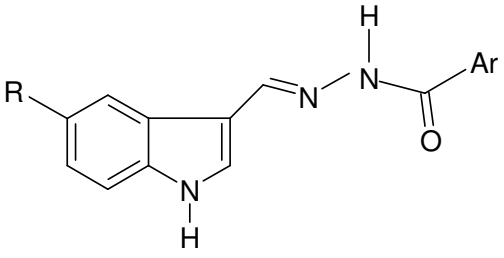

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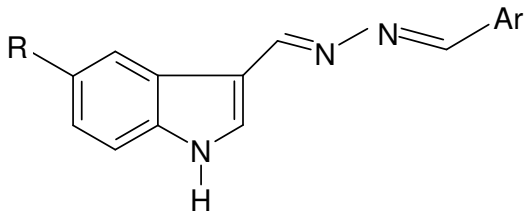
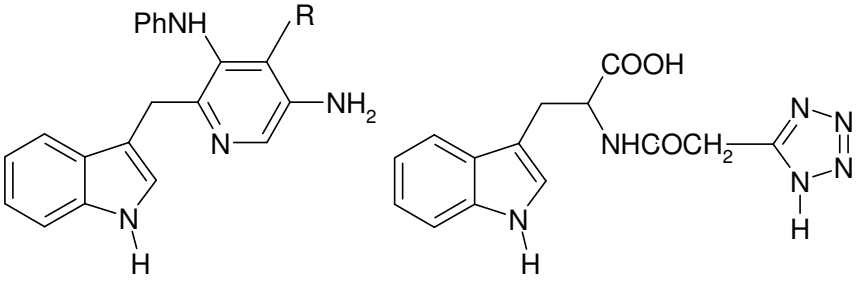


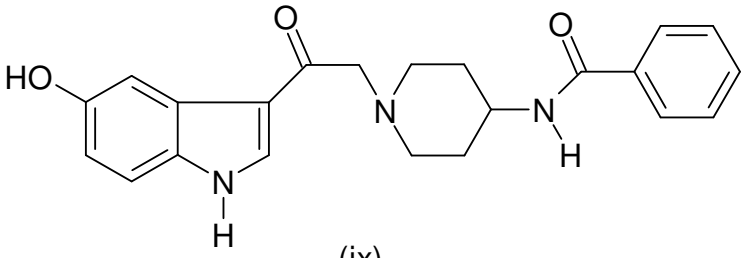
(vi)

Rafat MM et al[14], Synthesizing new substituted indole derivatives with structures justifying neuroprotective activity using L-tryptophan (TRP)as starting material in which they synthesized indolemethylpyridine derivatives(vii) and 2-(1H-tetrazole-5- methylencarboxamido)-3- (1H-indol-3-yl)propanonic acid (viii)the synthesized compound shown to possess antioxidant properties offering promising efficacy against oxidativestress induced by ACR administration.



(vii) (viii)

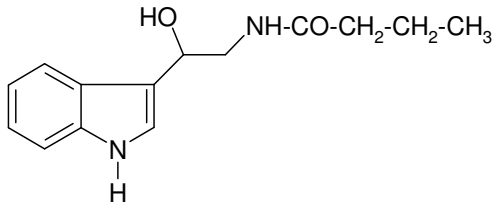
Maria Rosa Buemi[15]*et al*, carried out the molecular docking of several substituted indole derivatives in this process several derivatives are shows neuroprotective agent with antioxidant properties. In that, 4-dihydroxy-N-[1-[2-(5-hydroxy-1H-indol-3-yl)-2-oxoethyl]piperidin-4-yl]benzamide (ix) was the most effective antioxidant agent.



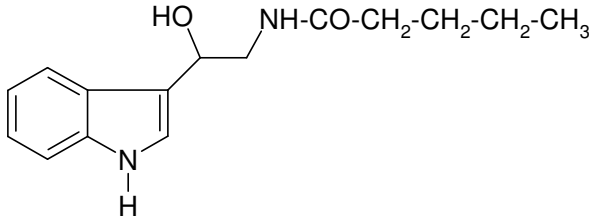
(ix)

Rudiger Faust *et al*[16],have synthesized several melatonin agonist and antagonist agent from 6*H*-Isoindolo[2,1-*a*]indoles,5,6-Dihydroindolo[2,1-*a*]isoquinolinesand6,7-Dihydro-5*H*-benzo[*c*]azepino[2,1-*a*]indoles.

K. Iakovou[17]*et al*, a series of new melatonin analogues has been synthesized. Interestingly, two of the newcompounds, (x)and (xi), which did not show any appreciable affinity for the melatoninreceptor, were found to be potent inhibitors of lipid peroxidation in rat liver microsomes.Analogue in particular is a better antioxidant than melatonin.



(X)



(xi)

AlessiaC[18]*et al*, have been synthesized several substituted Indole derivatives in which these compound screened for melatonin agonist agent.

Giorgio Tarzia[19]*et al*, new series of indole melatonin analogues, bearing the amidoethyl side chain attached atthe N-1 position of the indole nucleus, were synthesized and tested for their affinity for themelatonin receptor.

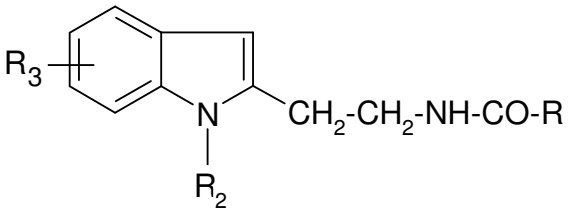
E. Duranti[20] *et al*, Synthesized the bromination of melatonin agent in which they found 2-Bromomelatonin behaved as apotent agonist in the physiological studies. It showed enhanced

activity in inhibitingthe spontaneous firing activity of cortical neurons and similarly to melatonin and2-iodomelatonin potentiated significantly the inhibitory effect of GABA.

Marco Mor[21]*et al*, have Synthesis of New Melatonin derivatives and Comprehensive Comparative Molecular Field Analysis (CoMFA) Study.

Silvia R[22]*et al*, have synthesized various derivatives of indole and carried out structure active relationship for MT_2 receptor.

Gilberto S[23] et al, have Design and carried QSAR studies of 2-*N*-Acylaminoalkylindoles (xii) as a MT_2-Selective Melatonin Antagonists.



(xii)

Silvia R[24]*et al*, reported the three-dimensional quantitative structure-activity relationship comparative molecular field analysis (3D-QSAR CoMFA) approach was applied to some synthesizes indole derivative classes of melatonin (MLT) membrane receptor ligand, with the principle aim of exploring the correlation between their steric features and MT_2-selective antagonism.

A careful inspection of a notable array of indole-containing compounds evidences the tryptamine & melatonin backbone as a common recognizable motive in the whole molecular structure.This study gives another perspective on antioxidant activities of synthetic melatonin analogues.

OBJECTIVE OF STUDY:-

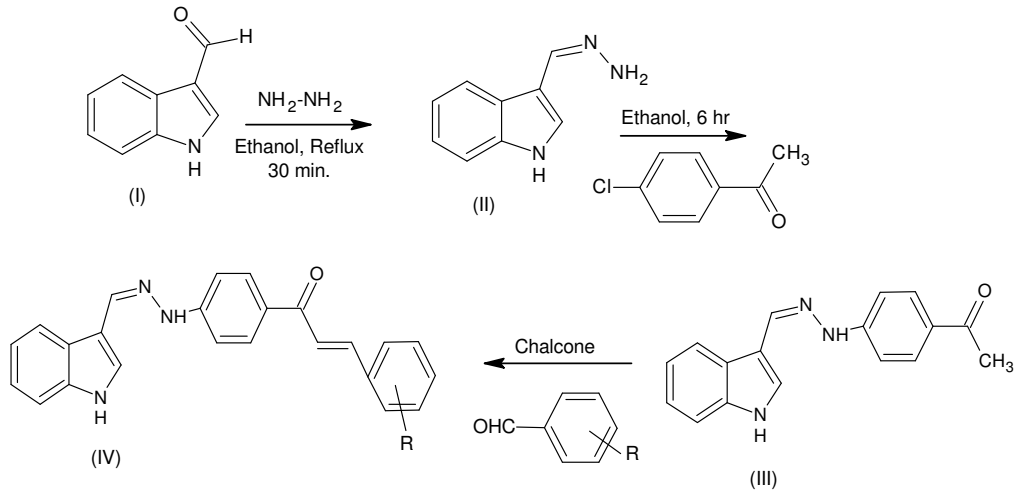
The present work is undertaken with the following objectives:

1. To synthesize novel molecules contains indole nucleus targeted for neuropathic pain.
2. To establish the structure of synthesized novel compound based on chemical and spectral data.
3. To carry out QSAR studies in order to optimize the structure for further development.
4. To carry out the Pharmacological activity study (against neuropathic pain) of novel synthesized compound.

MATERIAL AND METHODS:-

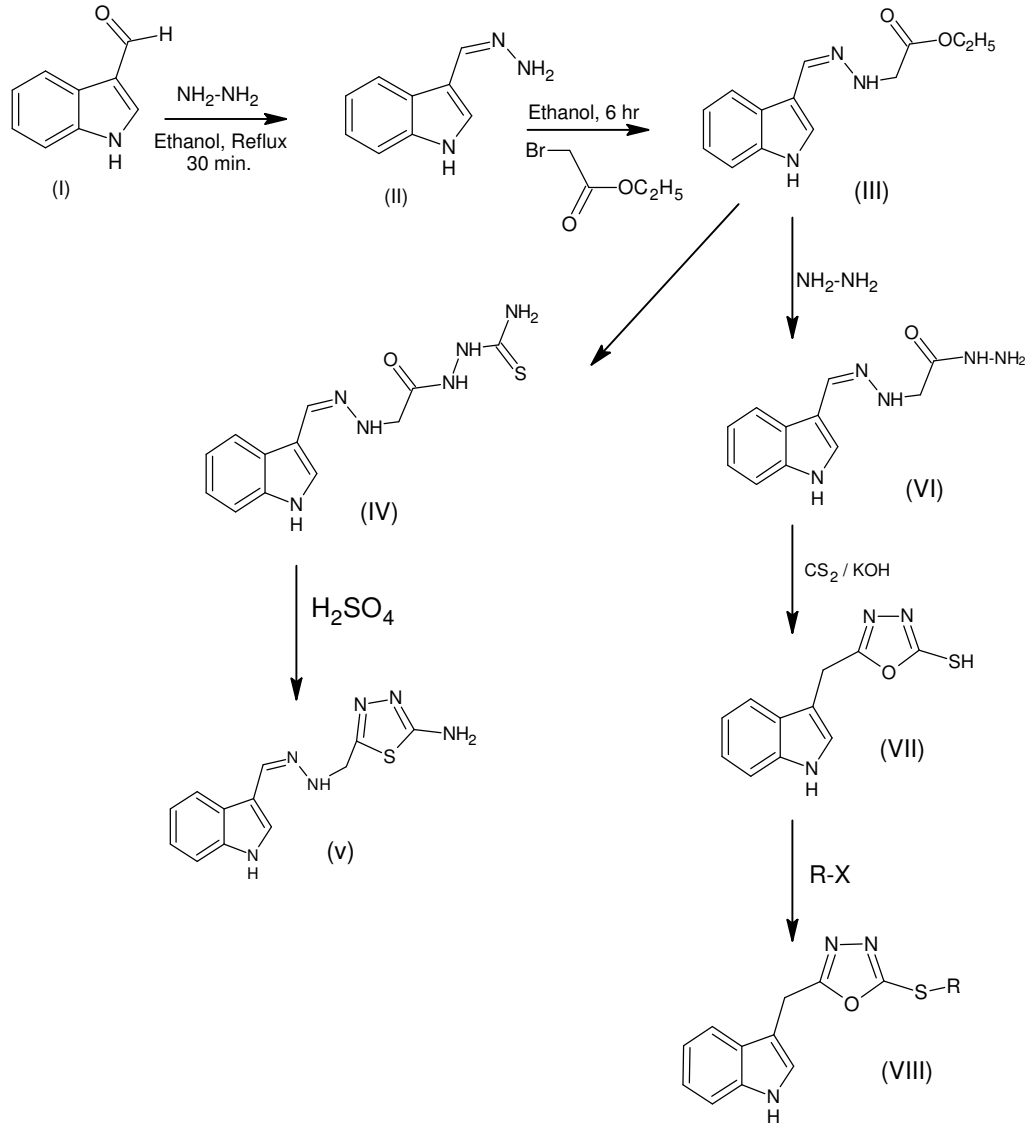
Proposed Synthetic Route–I

A mixture of Substituted indole 3-aldehyde (I) and hydrazine refluxed to yield hydrazide substitute indole (II), then hydrazide substituted indole is again reacted with p-chloro acetophenoneas result gives Indole Schiff base (III), which is further reacted with substituted benzaldehyde gives novel heterocyclic compound (IV) .



Proposed Synthetic Route–II

A mixture substituted indole-3-aldehyde (I)refluxed with hydrazine gives hydrazide substitute indole (II). When hydrazide substituted indole is reacted with bromo ethyl acetate as result gives substituted Indole Schiff base(III), it has further reacted with thiourea & later sulphuric acid gives indole substituted thiadiazole (V).An mixture of indole Schiff base reacted with Hydrazine & carbon dioxide as a product gives indole substituted oxdiazole (VIII) .



Characterization of Synthesized compound:

By Chromatographic &Spectroscopic techniques:

The synthesized compound will be purified by chromatographic techniques such as column chromatography, Preparative chromatography.

The compound synthesized will be characterized by UV, IR, NMR and Mass spectral data. This will be collected by sending the sample to other advanced research Centre like NCL, Pune.

The chemical structure of the synthesized compounds is established on the basis of Physical, chemical and analytical data, melting point of synthesized compound is determined in one capillary tube and is uncorrected. They expressed in degree centigrade.

The main objective of the present investigation is to explore newer heterocyclic molecule with potent Pharmacological activity.

QSAR investigation:-

1. To carry out QSAR studies for optimizing structure active relationship of functional groups present in a leading structure in terms of their biological endpoint[27].
2. Quantitative structure activity relationship (QSAR) is an attempt correlate structure descriptor of molecule with their physicochemical propertiesand biological activities.
3. Docking is a tool used in computational drug design predicting whether a particular compound will be a good inhibitor of particular protein[28].
4. QSAR studies use to reduce the time and money for drug design.
5. QSAR currently are being applied in many discipline, with many pertaining to drug design the main step implicated in this method include data collection, molecular description selection and procurement,correlation model developmentand finally model evolution.

6. To understand the relationship between structure and biological activity,for synthesized ring substituted derivatives a QSAR analysis will be carried out by generation of any possible QSAR model [29].
7. The QSAR investigation will carry out by VLIFE, Schrödinger and other suitable software.

PharmacologicalEvaluation:-

With an aim to explore the Pharmacological profile, the synthesized compound will be evaluated by possible activities for neuropathic pain.

For Pharmacological screening we use one of the following suitable model Streptozocin induced neuropathic pain model/Chronic constriction injury (CCI)/ Dioxane induced model/ Partial sciatic nerve ligation[30].

Source of data

The survey of literature on the area of present investigation will be done by referring to chemical abstract, all the national and international, journal to synthetic, medicinal and pharmaceutical chemistry.

The information about a pharmacological & biological activities will be collected by referring to Indian journal of Pharmacology, Indian journal of physiology and pharmacology, European journal of Pharmacology etc for this purpose, Library facility are available in our College, University, Indian Institute of Science, Bangalore, National Chemical Laboratory, Pune.

The day to day development in the area will be updated by Literature survey through e-publishing, Internet and current periodical in our library and elsewhere.

All the basic facilities required for the synthetic pharmaceutical chemistry are available in our research centre laboratories.

Scheme for proposed research work:-

Sr. No	RESEARCH WORK	TENTATIVE TIME IN MONTH
1	Literature Survey	03
2	Design of New compound & synthesis Planning	02
3	Procurement of drug, Chemicals and setting up the method for synthesis of title compound.	01
4	Synthesis of newer compound through VLIFE, Schrodinger QSAR suggestion	16
5	Purification and characterization of the new synthesized compounds A. Melting point determination B. Determination of IR, Mass and NMR spectra. C. Elemental analysis	03
6	QSAR investigation	03
7	Pharmacological evaluation of synthesized drug	05
8	Completion of research work and thesis writing	03

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